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A Rapid Method for Estimating Log P for Organic Chemicals

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A rapid, inexpensive technique based on reverse-phase high pressure liquid chromatography has been developed to estimate the n-octanol/water partition coefficient of organic chemicals. The system consists of a preparative Micro-Pak C-10^{R} reverse-phase column eluted with a 15 percent water/85 percent methanol solvent flowing at 2 ml/min at room temperature. The chemicals are detected in the eluant with a standard ultraviolet detector or a fraction collector system followed by appropriate analysis of the fractions to determine the retention time of the chemical. A linear calibration of the logarithm of retention time with the logarithm of the partition coefficient (Log P) is attained by using a mixture of benzene, bromobenzene, biphenyl, bibenzyl, pp'DDE, and 2,4,5,2',5' pentachlorobiphenyl as reference standards of known Log P. Chemicals with Log P of approximately 3 elute in less than 10 min whereas those with Log P greater than 5 elute after 20 min.

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FOREWORD

Many of the test protocols for screening organic chemicals for potential harmful effects in the environment rely on correlations of known effects with physical properties of the chemicals. The partition coefficient of a chemical in an n-octanol/water system provides insight into the tendency of chemicals to accumulate in lipoid tissues, to adsorb onto particulate matter coated with natural organic material, and to resist biodegradation. Specific correlations exist between the partition coefficient (expressed as Log P), the water solubility, and the bioconcentration factor of organic chemicals in fish. This report sets forth a rapid, inexpensive method for estimating Log P, which will greatly enhance screening tests for evaluating the potential hazards of chemicals in the environment.

ABSTRACT

A rapid, inexpensive technique based on reverse-phase high pressure liquid chromatography has been developed to estimate the n-octanol/water partition coefficient of organic chemicals. The system consists of a preparative Micro-Pak C-10® reverse-phase column eluted with a 15 percent water/85 percent methanol solvent flowing at 2 ml/min at room temperature. The chemicals are detected in the eluant with a standard ultraviolet detector or a fraction collector system followed by appropriate analysis of the fractions to determine the retention time of the chemical. A linear calibration of the logarithm of retention time with the logarithm of the partition coefficient (Log P) is attained by using a mixture of benzene, bromobenzene, biphenyl, bibenzyl, pp'DDE, and 2,4,5,2',5' pentachlorobiphenyl as reference standards of known Log P. Chemicals with Log P of approximately 3 elute in less than 10 min whereas those with Log P greater than 5 elute after 20 min.

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SECTION 1

INTRODUCTION

The use of the n-octanol/water partition coefficients (expressed as Log P) has become the cornerstone of predicting the biological effects of organic chemicals from physical properties through the use of structure-activity correlations (1, 2). The Log P value has become a critical physical property for predicting toxicity to aquatic organisms (3), bioconcentration factors for fish (4), and water solubility (5). Moreover, adsorption of chemicals in sewage sludges and organic particulate matter and the biodegradability of organic chemicals appear to be related to the Log P value.

Several methods can be used for measuring or estimating P. The obvious method is to mix the chemical with n-octanol and water, shake the biphasic system to assure equilibrium, and measure the concentration of the chemical in the two phases. The value of P is calculated as the ratio of the concentration in the octanol and the concentration in the water. This method can be laborious because emulsions are formed and analytical methods are needed for each chemical in at least one of the phases. The use of radiolabeled chemicals simplifies the analytical problems, but it may greatly increase the cost of the measurement. Also, chemicals with Log P of 4 and greater (10,000 times more in the octanol than water) cannot be measured with the same precision as chemicals that distribute more evenly, and highly lipid soluble chemicals are those of great concern in environmental hazard assessment. Another drawback to measuring P is that the measurement cannot be done reliably when dealing with mixtures of chemicals of unknown identity, such as would be encountered in complex effluents, because the bulk of the organic constituents may alter the solvent-system behavior.

If the structure of a chemical is known, Log P can be estimated from substituent constants as discussed by Hansch and Fujita (7). This is probably the best initial step in determining Log P since it can be done without experimentation and is quite reliable for many common organic chemicals. However, for some functional groups the substituent-constant approach is not yet completely reliable (Personal Communication, 1977, A. Leo, Pomona College, Claremount, Calif.) Moreover, the structure of the chemicals must be known, which precludes this approach from use in assessing potential hazards of complex effluents, landfill leachates, or other uncharacterized mixtures of chemicals.

The objectives of this study were to determine if Log P and the high pressure liquid chromatography (HPLC) reverse-phase retention time are related by using a wide variety of industrial chemicals, and, if so, to develop a method for estimating Log P by using HPLC. The results are

summarized in this report, and a method of estimating Log P is suggested which alleviates some of the problems discussed above. The constraints on this research were that the method be inexpensive, require less than 1 hr of laboratory time, and provide an acceptable measure of Log P.

SECTION 2

CONCLUSIONS

1. The logarithm of the retention time (Log RT) of organic chemicals on a permanently bonded (C-18) reverse-phase high pressure liquid chromatography system is linearly related to the logarithm of the n-octanol/water partition coefficient (Log P). The relationship is summarized by the equation Log P = 5.106 Log RT - 1.258 with a correlation coefficient 0.975.

2. By using a calibration mixture, the Log P of other organic chemicals were estimated with a mean accuracy of 22.8 percent compared to Log P values reported in the literature. The technique permits estimation of Log P in a maximum of 25 min and does not require a knowledge of the structure of the chemical for the estimate.

SECTION 3

RECOMMENDATIONS

1. The correlation between the estimates of Log P from the technique presented in this report and the Log P values from direct measurement is presently limited by the number of chemicals tested, particularly high lipophilic chemicals. Additional work is needed to expand the correlation and set confidence intervals for estimates of Log P by this indirect method.

2. The relationship between the dissociation constant of organic chemicals and the estimation of Log P by this indirect method is needed to evaluate the comparatively large discrepancies between estimated and literature Log P values for such chemicals.

SECTION 4

EXPERIMENTAL PROCEDURES

Reverse-phase liquid chromatography is a separation process in which chemicals are injected onto a column of fine particles coated with a nonpolar (water-insoluble) oil and then eluted with a polar solvent such as water or methanol. Recent developments in this field have produced a permanently bonded reverse-phase column in which long-chain hydrocarbon groups are chemically bonded to the column packing material resulting in a much more reproducible separation. The chemicals injected are moved along the column by partitioning between the mobile phase and the stationary hydrocarbon phase. Provided the residual polar groups on the packing can be kept at a minimum, mixtures of chemicals can be eluted in order of the hydrophobicity, with water-soluble chemicals eluted first and the oil-soluble chemicals last in proportion to their hydrocarbon/water partition coefficient. These experiments were intended to determine the relationship of the retention time on this reverse-phase column and the n-octanol/water partition coefficient.

LIQUID CHROMATOGRAPHY CONDITIONS

The liquid chromatograph was a Varian 4200 instrument equipped with two 5,000-psi pumps and a high pressure stopflow injector. The column was a Varian Micropak® C-10 analytical reverse phase column (250 mm x 2 mm I.D.) or a Preparative Micropak® C-H column (250 mm x 8 mm I.D.), which consists of a stainless tube filled with 10-μ Lichrosorb to which octadecylsilane is permanently bonded. The detector was a 254-nm ultraviolet detector with a 8-μl cell volume and 1-cm path length. The detector was interfaced with a Hewlett-Packard computer for retention-time determination. For chemicals that cannot be detected by the ultraviolet detector, a fraction collector was used to collect fractions at 1.0-min intervals for analysis by gas chromatography, liquid scintillation, or other suitable techniques.

The analytical column was operated at 50° C with a constant temperature bath. The solvent was programmed from 22 percent methanol in water initially to 75 percent methanol in water at a rate of 2 percent/min. The solvent flow rate was maintained at 20 ml/min at a pressure of approximately 2,500 psi.

The preparative column was operated at ambient temperature. The column was eluted isocratically with a mixture of water and methanol (15:85, v/v) which was pumped through the column at 2.0 ml/min at a pressure of approximately 1,200 psi.

TEST SOLUTIONS

Chemicals to be tested were dissolved in a mixture of acetone and cyclohexane (3:1, v/v), which was found to be suitable for compounds over a wide range of water solubility. Because only the retention time of the chemical, which is independent of concentration in dilute solutions, is used in this method, the quantity of individual chemicals in the solution was adjusted to give a chromatographic peak of at least 25 percent of the recorder scale.

CALIBRATION MIXTURE

Six chemicals for which Log P has been reported were used to calibrate the elution time in units of Log P. The calibration mixture includes benzene, bromobenzene, biphenyl, bibenzyl, pp'DDE, and 2,4,5,2',5' pentachlorobiphenyl. The Log P values selected from the literature for these chemicals were 2.13, 2.99, 4.09, 4.81, 5.69, and 6.11, respectively. (References for Log P values are given in Table 1.)

SECTION 5

RESULTS AND DISCUSSION

CORRELATION OF LOG P AND HPLC RETENTION

Previous work at this laboratory (6) has shown that the reported values of Log P for a wide variety of organic chemicals are correlated to the retention volume of the chemical in the reverse-phase HPLC column. The data obtained by using the gradient elution with the analytical column (2 mm I.D.) are summarized in Table 1. In this table, the retention volume, K, is corrected for minor column variations by using phenol as an internal standard and setting its retention equal to 1.00. The log K values are presented relative to the K value of phenol.

The Log P values were taken from Leo, Hansch, and Elkins (8) except for those of the PCB. Because these formulations (the Aroclor's) consist as mixtures, the log K values are presented as ranges of values obtained for the major component peaks observed in the HPLC chromatograms. The Log P values for PCB's are those provided by Chiou et al. (5) for PCB's having three to six chlorine atoms per molecule. The Log P values used for the Aroclor's were: Aroclor 1016 and Aroclor 1242, 5.58; Aroclor 1248, 6.11; and Aroclor 1254, 6.72 (Table 1). Although these values are only approximations, the possible deviation must be small since the entire range for these PCB's is small.

The data in Table 1 were analyzed by a family regression procedure as illustrated in Figure 1. The data can best be summarized by power function of Log P = $a(\log K)^b$, where a and b are constants with r^2 for the correlation equal to 0.870. Although this variance may seem somewhat large, the correlation includes ketones, aldehydes, phenols, aromatic amines, ethers, aromatic hydrocarbons, and a variety of chlorinated hydrocarbons that span over six orders of magnitude of lipophilic properties. The relationship between Log P and log K is best approximated with a power function because of the solvent gradient used with the analytical column to optimize resolution. The solvent gradient increases the methanol concentration during the analysis, and the retention of highly lipophilic chemicals is less than that which would have resulted by using a constant solvent composition.

Having demonstrated a strong correlation between Log P and the HPLC relative retention time, the secondary objectives of developing a simple method for calculating Log P from retention times and reducing the cost of the analysis were pursued. The use of phenol as an internal standard was judged too tedious, and the non-linear correlation resulting from the gradient elution increased both the cost and the complexity of the analysis. The use of isocratic elution

TABLE 1. RETENTION DATA OF A VARIETY OF CHEMICALS OBTAINED BY USING GRADIENT ELUTION REVERSE-PHASE HPLC

Chemical	K (phenol=1.00)	Log K (phenol=0.00)	Log P
Hydroquionone	0.27	-0.564	0.59
m-Aminophenol	0.36	-0.439	0.17
Resorcinol	0.36	-0.439	0.80
Catechol	0.73	-0.138	0.95
Phenol	1.00	0.000	1.46
o-Aminophenol	1.00	0.000	0.62
4-Methoxyphenol	1.17	0.067	1.34
Aniline	1.18	0.073	0.98
Benzyl Alcohol	1.40	0.146	1.10
o-Toludine	1.82	0.260	1.32
4-Nitrophenol	1.83	0.263	1.91
o-Anisidine	2.00	0.301	0.95
Benzaldehyde	2.18	0.338	1.48
3-Methylphenol	2.25	0.352	1.96
2-Phenylethanol	2.27	0.357	1.60
4-Methylphenol	2.33	0.368	1.94
Indole	2.45	0.390	2.25
o-Chloroaniline	2.48	0.395	1.92
Benzene	2.50	0.398	2.13
n-Methylaniline	2.90	0.464	1.82
Acatophenone	3.18	0.503	1.58
Cinnamyl Alcohol	3.32	0.521	1.95
4-Chlorophenol	3.73	0.571	2.39
Anisole	4.00	0.602	2.11
2,4-Dimethylphenol	4.00	0.602	2.36
Dimethylphthalate	5.42	0.734	2.11
1-Naphthol	6.46	0.810	2.98
3-Methyl-4-Chlorophenol	7.04	0.848	3.10
2,4-Dichlorophenol	8.73	0.941	3.08
Pentachlorophenol	10.42	1.018	5.01
4-Phenylphenol	11.46	1.059	3.37
Diethylphthalate	12.45	1.095	3.15
Naphthalene	12.65	1.103	3.37
2,4,5-Trichlorophenol	14.27	1.154	3.72
Diphenylamine	14.36	1.157	3.50
Diphenylether	18.50	1.267	4.21
Anthracene	22.33	1.344	4.45
n,n-Dibutylphthalate	24.45	1.388	5.15
p,p'-Methoxyclor	39.81	1.600	4.20
Endrin	39.82	1.600	4.56
p,p'-DDD	41.70	1.620	6.02
p,p'-DDT	44.69	1.650	6.19
Hexachlorobenzene	52.50	1.72	6.18
Aroclor 1016	35.50-51.30	1.55-1.71	5.58
Aroclor 1242	25.50-60.29	1.55-1.78	5.58
Aroclor 1248	35.50-60.28	1.55-1.78	6.11
Aroclor 1254	35.50-69.20	1.55-1.84	6.72

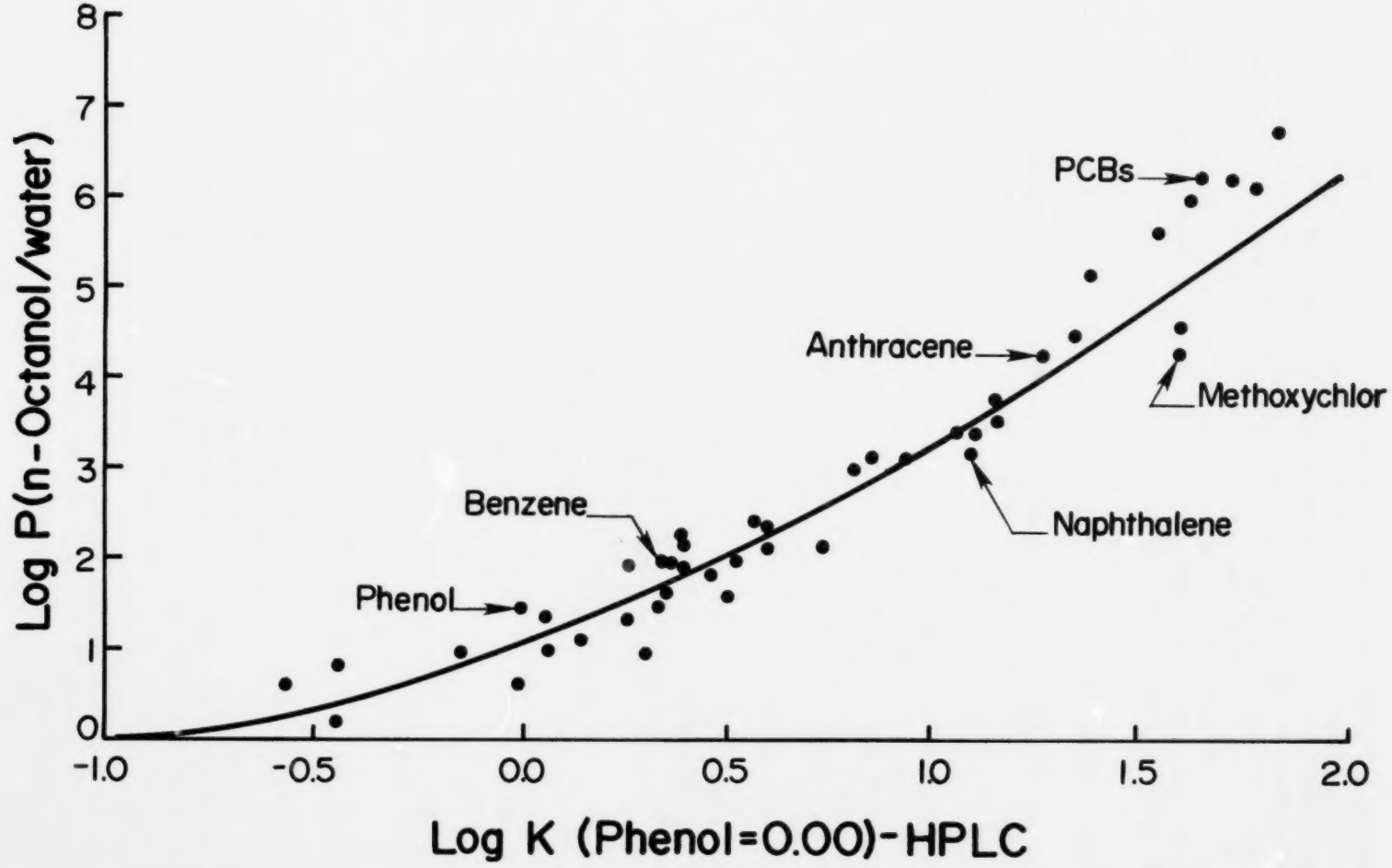

Figure 1. Verification of the dpendency of the HPLC relative retention time on the Log P for 47 organic Chemicals.

resulted in a linear correlation and the development of a simple calibration mixture to replace the internal standard. Although the analysis time increases when the isocratic elution is used, substantial savings are possible because it eliminates the need for one of the HPLC pumps and the electronic solvent programming module (approximately 50 percent of the instrument costs). Finally, preparative scale reverse-phase columns produce linear calibration curves with shorter overall retention times at pressures of only 1,200 psi. This column offers the additional advantage of a larger loading capacity which is needed for analysis of complex effluents.

CALCULATION OF LOG P

The calibration mixture is chromatographed on the preparative column, and a calibration curve is prepared daily to eliminate small differences due to flow rate or temperature and to follow the retention properties of the column during prolonged use. The calibration is made by plotting the Log P versus the logarithm of the absolute retention time (Log RT). Figure 2 presents the data from Table 2 in the form of the calibration curve. The relationship between Log P and log RT can be fitted equally well by using a linear or a parabolic function when these data are plotted. However, the linear regression is more convenient to use in daily calculations, and differences between the linear and exponential models appear only if Log P is estimated by extrapolating beyond the range of Log P values used in the calibration.

The data in Figure 2 can be summarized with the equation Log P = 5.106 Log RT - 1.258, with a correlation coefficient of 0.975. The relative standard deviations of the slope, intercept, and correlation coefficient of seven calibration curves during a 2-week period were approximately 1 percent, 14 percent, and 0.1 percent, respectively. It must be emphasized that this correlation is limited in regard to being representative of the organic chemicals encountered. The calibration mixture was selected largely on the basis of Log P values reported in the literature, and the correlation appears to be linear over five orders of magnitude of this chemical property. Although the accuracy of the estimates might be more convincing if several hundred chemicals were presented in the correlation, it would be unmanageable to prepare such a calibration mixture and use it daily in the calibration of the liquid chromatograph.

HPLC ESTIMATION OF LOG P

To determine the accuracy of the calibrated liquid chromatographic method of estimating Log P by comparison with data reported in the literature, the retention times of 18 chemicals, including the standards, were determined, and the Log P values were calculated from the regression equation. Table 3 presents the results of these estimates. The data show that Log P can be estimated with a mean accuracy of 22.5±20.1 percent of the values reported in the literature obtained by using other methods. The percent error in Table 3 was calculated assuming that the literature value is the correct value for Log P. The mean absolute error in Log P for this set of chemicals was 0.64. This error is approximately twice the error that can be expected by calculation with the

TABLE 2. HPLC RETENTION TIMES AND PARTITION COEFFICIENTS FOR ORGANIC CHEMICALS USED FOR CALIBRATION

Chemical	Retention time (min)	Log RT	Log P (ref.)
Benzene	4.12	0.615	2.13 (7)
Bromobenzene	7.09	0.851	2.99 (5)
Biphenyl	8.85	0.947	3.76[a] (7)
Bibenzyl	15.87	1.201	4.81[a] (7)
pp'DDE	21.98	1.342	5.69 (5)
2,4,5,2',5' pentachlorobiphenyl	31.58	1.499	6.11 (5)

[a] Mean of Log P values reported.

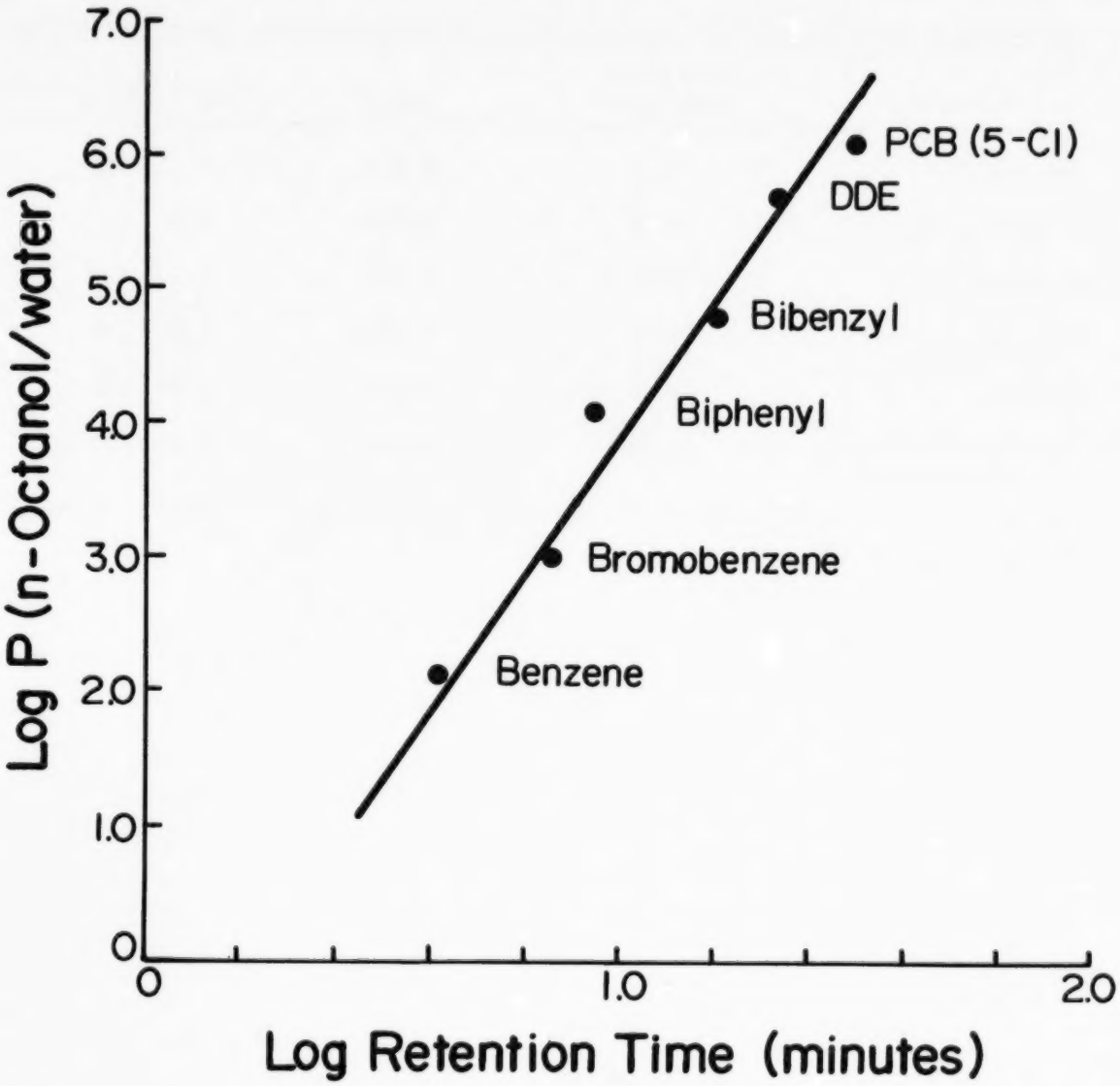

Figure 2. Relationship between Log P and HPLC log retention time of the calibration mixture.

substituent constants approach (Leo, personal communication); However, the structure of the chemical need not be known to estimate the lipophilic properties with the HPLC method.

Table 3 also shows that some of the greatest relative errors are observed with polar chemicals which dissociate in water. The data indicate that the dissociation of ionizable polar groups is more significant than adsorption interactions since chemicals such as m-chlorobenzoic acid, 2,4,5-trichlorophenol, and diphenylomine elute more rapidly than would be expected from their respective Log P values. One explanation of this observation is that these chemicals are dissociated in the unbuffered solvent and behave, in part, as ions in the elution. This may be corrected by selecting a series of buffer solvents for organic acids and bases which assure that the chemical would be in the un-ionized form. However, considerable research is required before a rationale involving buffer systems can be evaluated with a broad range of chemicals.

TABLE 3. COMPARISON OF ESTIMATED LOG P VALUES

WITH REPORTED LOG P VALUES FOR 18 ORGANIC CHEMICALS

Chemical	Reported Log P	Estimated Log P	Absolute deviation	Percentage deviation
o-Toluidine	1.32	1.63	0.31	23.5
Benzaldehyde	1.48	2.33	0.85	47.7
Nitrobenzene	1.86	1.82	0.04	2.2
p-Nitrophenol	1.91	1.35	0.56	29.3
Dimethylphthalate	2.11	3.40	1.29	61.1
Benzene	2.13	2.39	0.26	12.2
Indole	2.25	1.66	0.59	26.2
m-Chlorobenzoic acid	2.68	0.89	1.79	66.8
Bromobenzene	2.99	2.92	0.07	2.3
Methoxychlor	4.20	3.82	0.42	10.0
Naphthalene	3.41	3.17	0.24	7.0
Diphenylamine	3.50	2.37	1.13	30.4
2,4,5-Trichlorophenol	3.72	2.39	1.33	35.6
Biphenyl	3.76	3.75	0.01	0.3
Anthracene	4.45	3.45	1.00	22.5
p,p'-DDE	5.69	5.83	0.14	2.5
2,4,5,2',5' PCB	6.11	6.44	0.33	5.4
Hexachlorobenzene	6.18	7.42	1.24	20.1
Mean Standard Deviation			0.64 ± 0.54	22.5 ± 20.1

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